REMARKS

The office action dated May 9, 2001 has been carefully considered. It is believed that the claim amendments and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim Objections

The Examiner has objected to claim 26 which is dependent on claim 23 on the basis that claim 23 is absent. In addition, the Examiner alleges that there are no claims 23-25. We respectfully disagree with the Examiner for the reasons that follow.

There are 26 claims in the application presently on file. In response to the Written Opinion provided by the International Preliminary Examination Authority, claims 1-21 were amended to claims 1-26. Thereafter, a preliminary amendment was filed when we entered the national phase for PCT/CA98/00325 in the United States Patent and Trademark Office on October 7, 1999. Claims 23-25 were not mentioned in the preliminary amendment as they were not amended. However, claims 23-25 were not deleted by the Applicant and should still remain on file. We submit that no correction is required.

35 USC §112, second paragraph

The Examiner has objected to claims 1-22 and 26 under 35 USC §112, second paragraph, as being indefinite because it is unclear how to define "increase the serum life". In response, we submit that one of skill in the art would understand readily what is meant by "increase the serum half-life" especially with reference to the disclosure. For example on page 15, lines 6-10 of the specification, the phrase "sufficient to increase serum half-life of the immune globulin" is clearly defined to mean that the serum half-life of the immune globulin with the surface active agent is increased as compared to the serum half-life of an immune globulin without a surface active agent.

The Examiner has objected to claims 19 and 21 as vague and indefinite because it is unclear how to define "to reduce the elevation of neutrophil counts". In response, we submit that a person skilled in the art would readily understand what is meant by the expression "to reduce the elevation of neutrophil counts" as found for example on page 15, lines 31-32 and page 16, lines 1-2 of the specification, and, as such, is clear to those skilled in the art. In particular, the specification clearly describes that the reduction of neutrophil counts is in comparison to a preparation without a surface active agent.

In view of the foregoing, we respectfully request that the objections to the claims under 35 USC §112, second paragraph be withdrawn.

35 USC §102

The Examiner has objected to claims 1, 7, 9-12, 14-15, 18 and 20 under 35 USC §102(b) as being anticipated by Beggs et al. (WO 95/01155). We respectfully disagree with the Examiner for the reasons that follow.

Beggs et al. describes an oral care composition comprising an antibody and a surfactant. We submit that the entire disclosure of Beggs et al. is directed to oral therapeutics and makes no mention of any use whatsoever of an antibody non-ionic surfactant combination for intravenous administration. By the present amendment, independent claims 1 and 23 have been amended in order to specify that the immune globulin preparation is an intravenous immune globulin preparation.

The Examiner has objected to claims 1, 7, 9-12, 14-15, 17-20 and 22 under 35 USC § 102(b) as being anticipated by Hirao et al. (EP 278,422). We respectfully disagree with the Examiner for the reasons that follow.

Hirao et al. discloses injectable solutions of γ-globulin containing **sorbitol** as a stabilizer and having a low electrical conductivity. Sorbitol is not a non-ionic surfactant. Evidence

for properties of sorbitol and sorbitan esters can be found for example in the following reference which can be provided to the Examiner upon request:

> A. Wade and P.J. Weller, Handbook of Pharmaceutical Excipients, 1994, 2nd ed., American Pharmaceutical Association, Washington, DC pp 477-480, pp 207-208, pp 375-378, pp 473-476.

The use of non-ionic surfactants such as **sorbitan** esters to improve the compatibility with antibody to improve the serum half-life of an antibody disclosed or suggested in Hirao et al.

The Examiner states that on page 2 lines 30-36 Hirao et al. teaches the use of sorbitan as a stabilizer in an injectable solution. We respectfully disagree. On page 2, line 36, Hirao specifically states "said solution further containing **sorbitol**". The entire disclosure makes no mention of any use of soribitan or a sorbitan/antibody combination for intravenous administration.

In view of the foregoing, we respectfully request that the objections to the claims under 35 USC §102 be withdrawn.

We point out that both Beggs et al. and Hirao et al. were cited during prosecution of the corresponding PCT application. The Examiner concluded in the International Preliminary Examination Report that the claims are novel and inventive over both references.

35 USC § 103

The Examiner has objected to claims 2-4, 8, 15-17, 19-20, 22 and 26 under 35 USC § 103(a) as being unpatentable over Beggs et al. (WO 95/01155) in view of Friesen (CA 1,168,152). We respectfully disagree with the Examiner for the reasons that follow.

The inventors have surprisingly found that the inclusion of a non-ionic surface active agent in an immune globulin preparation prolong the serum half-life of the immune globulin in vivo. A longer serum half-life in vivo is clearly advantageous as it means that

the immune globulin preparation will have a longer survival time in the blood stream to assert its therapeutic effect which will allow for reduced frequency of immune globulin administration. Traditionally, surface active agents have been used to improve product stability in storage (and not in vivo) and/or to increase product solubility. Importantly, in two separate studies, it had been shown that the inclusion of surface active agent in chemotherapeutic preparations actually reduce the serum half-life of the chemotherapeutic (see page 9, lines 11-21 of the application). Consequently, at the time of the invention, one of skill in the art would have predicted that the inclusion of a surface active agent in an immune globulin preparation would reduce and not increase the serum half-life.

As discussed above, Beggs et al. teaches an oral care composition of immune globulin containing a non-ionic surfactant and does not contemplate the intravenous administration of an immune globulin/non-ionic surfactant preparation. In addition, Beggs uses a non-ionic surfactant in his preparation to increase shelf life and not serum half-life.

Friesen teaches the preparation of human immune globulin (IgG) aqueous fraction for intravenous injection and the preparation of Rh immune globulin. Friesen does not teach or even remotely suggest that one could add non-ionic surfactant to the intravenous preparation to increase the serum half-life of the immune globulin in the bloodstream. In view of the known properties of non-ionic surface active agents to reduce the serum half-life, one skilled in the art after reading Friesen would in no way be motivated to include a non-ionic surfactant to a commercially available anti-RH_0 D immune globulin for intravenous administration.

The Examiner has objected to claims 5-7 under 35 USC § 103(a) as being unpatentable over Beggs et al. (WO 95/01155) in view of Moore. We respectfully disagree with the Examiner for the reasons that follow.

Our comments on Beggs et al. appear above. The deficiencies in Beggs are not remedied by Moore.

Moore teaches antibody detection and quantitation in the technicon autoanalyzer from serum. Moore does not teach or even remotely suggest that one could add non-ionic surfactant to an intravenous preparation of anti-c immune globulin to increase the half-life of anti-c immune globulin *in vivo*. In fact, Moore simply notes anti-c immune globulin detection in human serum.

The Examiner has objected to claim 13 under 35 USC § 103(a) as being unpatentable over Beggs et al. (WO 95/01155) in view of Jansen (EP 318,081). We respectfully disagree with the Examiner for the reasons that follow.

Our comments on Beggs et al. appear above. The deficiencies in Beggs are not remedied by Jansen.

Jansen teaches the use of a polyoxypropylene-polyoxyethylene block polymer and a phospolipid or a mixture of two or more of these components to stabilize aqueous solutions of antibodies. In the specification, the reference specifically discloses the use of block polymer and a phospolipid mixture for commercial purposes with improved storage stability. In contrast, the Applicants' claim 13 teaches the use of one or more surfactants selected from a specific group of polyoxyethylene sorbitan fatty acid esters (polysorbates) to increase serum half-life of immune globulin *in vivo* following intravenous administration.

Polysorbates are a series of fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. Jansen does not teach or remotely suggest the use of polysorbates to increase serum half-life of immune globulin in preparations for intravenous administration. As a result, one skilled in the art after reading Jansen would in no way

be motivated to include polysorbates in intravenous preparations containing immune globulins to extend their serum survival time in the bloodstream.

In view of the above, we respectfully request that all of the objections to the claims under 35 USC § 103(a) be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

In view of the foregoing comments, we respectfully submit that the application is in order for allowance and early indication to that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact the undersigned by telephone at (416) 364-7311 at his convenience.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 1 and 23 have been amended as follows.

1. (Amended) An intravenous immune globulin preparation [for intravenous injection] comprising a hyperimmune globulin and at least one non-ionic surface active agent, said one or more non-ionic surface active agent(s) in a concentration sufficient to increase the serum half-life of the immune globulin.

23. (Amended) An intravenous immune globulin preparation comprising an immune globulin, having a purity of greater than about 95 percent and a monomeric protein content of greater than about 94 percent, and at least one non-ionic surface active agent, said one or more non-ionic surface active agent(s) in a concentration sufficient to increase the serum half life of the immune globulin.